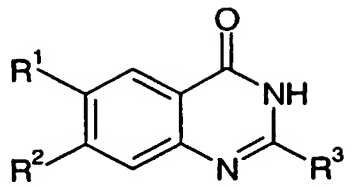
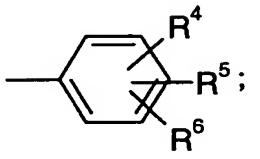
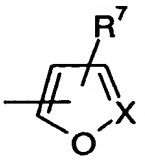
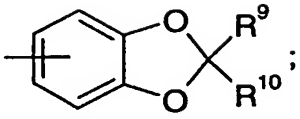
Claims

1. A quinazolinone of formula I



(I)

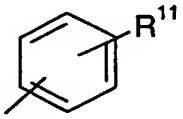
wherein

R^1 is hal;  ;  or  ;

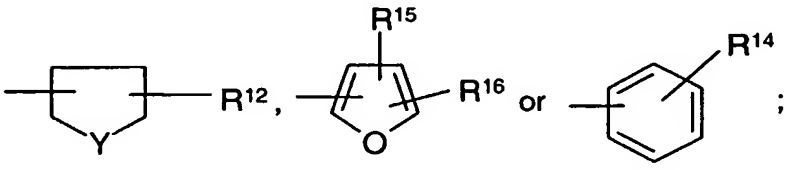
X is N or CR^8;

R^2 is hal; nitro; C_1-C_6alkylcarbonyl; C_1-C_6alkyl or C_3-C_6cycloalkyl;

R^3 is C_1-C_6alkyl; C_1-C_6alkoxy or amino;

R^4 is H; hal; hydroxy; amino; C_1-C_6alkyl-amino, di(C_1-C_6alkyl)-amino, C_1-C_6alkyl; C_1-C_6alkoxy which is unsubstituted or mono-, di- or trisubstituted by halogen or hydroxy; C_1-C_6alkoxyC_1-C_6alkoxy; C_1-C_6alkoxyC_1-C_6alkoxyC_1-C_6alkoxy; C_1-C_6alkoxyC_1-C_6alkyl; C_3-C_7cycloalkyl or C_3-C_7cycloalkylC_1-C_6alkoxy that may be substituted at the cycloalkyl residue by C_1-C_6alkyl; C_1-C_6alkoxycarbonyl; C_3-C_6alkenyloxy; (C_1-C_6alkyl)$_2$N-C_1-C_6alkoxy; C_1-C_6alkyl-sulfanyl; C_1-C_6alkyl-sulfanylC_1-C_6alkoxy,  or

-O-$[CH_2]_n$-A wherein A represents



Y represents O or NR^{13},

and n is 0, 1, 2, 3, 4, 5 or 6;

R^5 and R^6, independently, are H; hal; C_1-C_6alkoxy; or C_1-C_6alkyl;

R^7 and R^8, independently, are H or C_1-C_6alkyl;

R^9 and R^{10}, independently, are H or hal;

R^{11} is H; hal; C_1-C_6alkoxy; or C_1-C_6alkyl;

R^{12} is H; hal; C_1-C_6alkoxy; or C_1-C_6alkyl;

R^{13} is H or C_1-C_6alkyl;

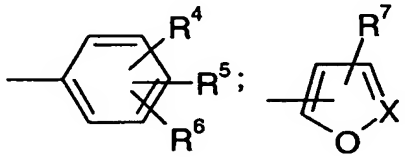
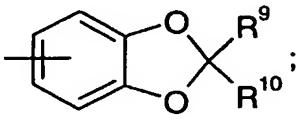
R^{14} is H; hal; C_1-C_6alkoxy; or C_1-C_6alkyl; and

R^{15} and R^{16}, independently, are H; hal; or C_1-C_6alkyl;

with the exception of the compound of formula I wherein R^1 and R^2 are both iodo or chloro and R^3 is methyl, and of the compound of formula I wherein R^1 and R^2 are both selected from fluoro and bromo and R^3 is butyl,

in free base or acid addition salt form.

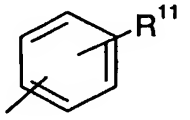
2. A quinazolinone of formula I according to claim 1 wherein

R^1 is hal;  or  ;

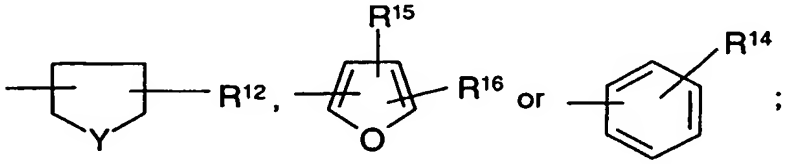
X is N or CR^8;

R^2 is C_1-C_6alkyl;

R^3 is C_1-C_6alkyl; C_1-C_6alkoxy or amino;

R^4 is H; hal; hydroxy; amino; C_1-C_6alkyl-amino, di(C_1-C_6alkyl)-amino, C_1-C_6alkyl; C_1-C_6alkoxy which is unsubstituted or mono-, di- or trisubstituted by halogen or hydroxy; C_1-C_6alkoxyC_1-C_6alkoxy; C_1-C_6alkoxyC_1-C_6alkoxyC_1-C_6alkoxy; C_1-C_6alkoxyC_1-C_6alkyl; C_3-C_7cycloalkyl or C_3-C_7cycloalkylC_1-C_6alkoxy that may be substituted at the cycloalkyl residue by C_1-C_6alkyl; C_1-C_6alkoxycarbonyl; C_3-C_6alkenyloxy; (C_1-C_6alkyl)$_2$N-C_1-C_6alkoxy; C_1-C_6alkyl-sulfanyl; C_1-C_6alkyl-sulfanylC_1-C_6alkoxy,  or

-O-$[CH_2]_n$-A wherein A represents

 ;

Y represents O or NR^{13},

and n is 0, 1, 2, 3, 4, 5 or 6;

R^5 and R^6, independently, are H; hal; C_1-C_6alkoxy; or C_1-C_6alkyl;

R^7 and R^8, independently, are H or C_1-C_6alkyl;

R^9 and R^{10}, independently, are H or hal;

R^{11} is H; hal; C_1-C_6alkoxy; or C_1-C_6alkyl;

R^{12} is H; hal; C_1-C_6alkoxy; or C_1-C_6alkyl;

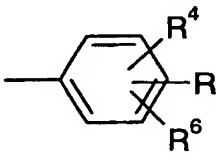
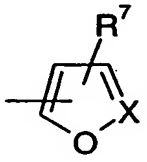
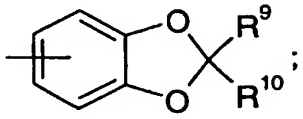
R^{13} is H or C_1-C_6alkyl;

R^{14} is H; hal; C_1-C_6alkoxy; or C_1-C_6alkyl; and

R^{15} and R^{16}, independently, are H; hal; or C_1-C_6alkyl;

in free base or acid addition salt form.

3. A quinazolinone of formula I according to claim 1 or 2 wherein

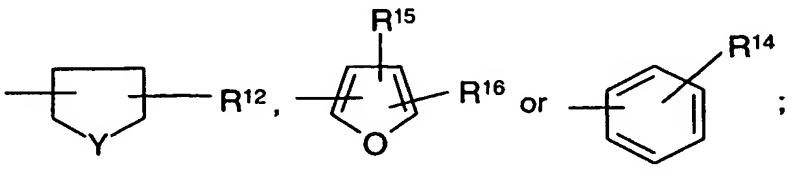
R^1 is hal;  ;  or  ;

X is N or CR^8;

R^2 is C_1-C_6alkyl;

R^3 is C_1-C_6alkyl or amino;

R^4 is hal; hydroxy; amino; C_1-C_6alkyl-amino, C_1-C_6alkyl; C_1-C_6alkoxy which is unsubstituted or monosubstituted by halogen or hydroxy; C_1-C_6alkoxyC_1-C_6alkoxy; C_1-C_6alkoxyC_1-C_6alkoxyC_1-C_6alkoxy; C_1-C_6alkoxyC_1-C_6alkyl; C_3-C_7cycloalkyl or C_3-C_7cycloalkylC_1-C_6alkoxy that may be substituted at the cycloalkyl residue by C_1-C_6alkyl; C_1-C_6alkoxycarbonyl; C_3-C_6alkenyloxy; $(C_1$-C_6alkyl$)_2$N-C_1-C_6alkoxy; C_1-C_6alkyl-sulfanyl; C_1-C_6alkyl-sulfanylC_1-C_6alkoxy, or -O-$[CH_2]_n$-A wherein A represents



Y represents O or NR^{13},

and n is 0, 1 or 2;

R^5 and R^6, independently, are H; hal; or C_1-C_6alkoxy;

R^7 and R^8, independently, are H or C_1-C_6alkyl;

R^9 and R^{10}, independently, are H or hal;

R^{12} is H;

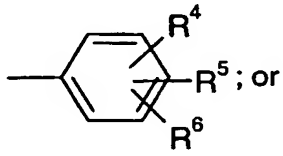
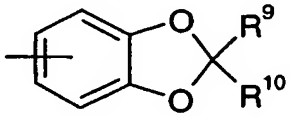
R^{13} is C_1-C_6alkyl;

R^{14} is H; or C_1-C_6alkoxy; and

R^{15} and R^{16} are H;

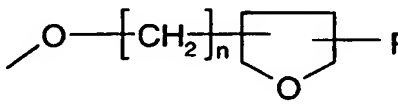
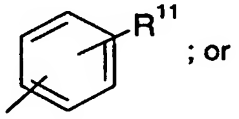
in free base or acid addition salt form.

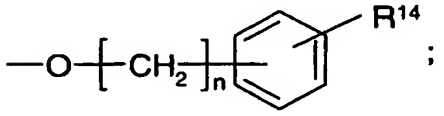
4. A compound of formula I according to claim 1 wherein

R^1 is hal;  ; or 

R^2 is hal; nitro; C_1-C_6alkylcarbonyl; C_1-C_6alkyl or C_3-C_6cycloalkyl;

R^3 is C_1-C_6alkyl; C_1-C_6alkoxy or amino;

R^4 is H; hal; hydroxy; C_1-C_6alkyl; C_1-C_6alkoxy; C_1-C_6alkoxyC_1-C_6alkoxy; C_1-C_6alkoxyC_1-C_6alkoxyC_1-C_6alkoxy; C_1-C_6alkoxyC_1-C_6alkyl; halogenoC_1-C_6alkoxy; C_3-C_7cycloalkylC_1-C_6alkoxy that may be substituted at the cycloalkyl residue by C_1-C_6alkyl; C_1-C_6alkoxycarbonyl; C_3-C_6alkenyloxy; $(C_1$-C_6alkyl$)_2$N-C_1-C_6alkoxy; C_1-C_6alkyl-sulfanyl; C_1-C_6alkyl-sulfanylC_1-C_6alkoxy,  ;  ; or

 ;

wherein n is 0, 1, 2, 3, 4, 5 or 6;

R^5, R^6, R^{11} and R^{14}, independently, are H; hal; C_1-C_6alkoxy; or C_1-C_6alkyl;

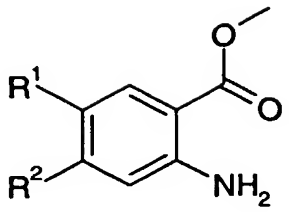
R^{12} is H or C_1-C_6alkyl; and

R^9 and R^{10}, independently, are H or hal;

with the exception of the compound of formula I wherein R^1 and R^2 are both iodo or chloro and R^3 is methyl, and of the compound of formula I wherein R^1 and R^2 are both selected from fluoro and bromo and R^3 is butyl,

in free base or acid addition salt form.

5. A compound of formula II



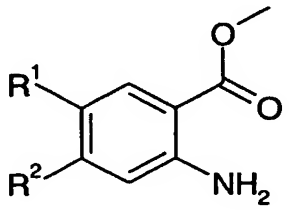
(II)

wherein

R^1 and R^2 are as defined in claim 1.

6. A process for the preparation of a compound of formula I as defined in claim 1, or a salt thereof, comprising the steps of

a) for the production of a compound of formula I wherein R^3 is not NH_2, reacting a compound of formula II

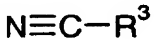


(II)

wherein

R^1 and R^2 are as defined in claim 1,

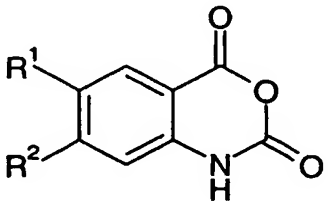
with a compound of formula III



(III)

wherein R^3 is as defined in claim 1; or

b) for the production of a compound of formula I wherein R^3 is NH_2, reacting a compound of formula IV

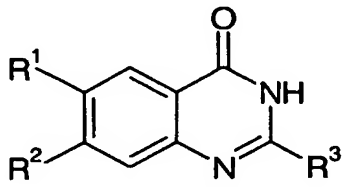


(IV)

wherein R^1 and R^2 is as defined in claim 1,
with 2-ethyl-2-thiopseudourea hydrobromide;
and recovering the obtained compound, in free or in salt form.

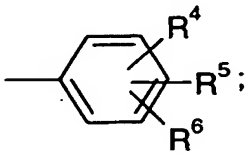
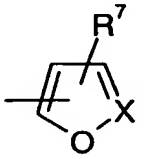
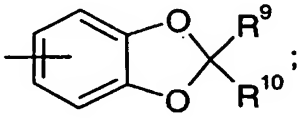
7. A compound of any one of claims 1 to 4 in free base or pharmaceutically acceptable acid addition salt form, for use as a pharmaceutical.

8. A quinazolinone of formula I



(I)

wherein

R^1 is hal;  ;  or  ;

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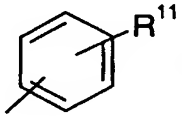
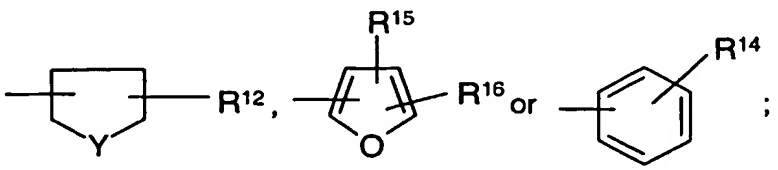
R^3 is C_1-C_6alkyl; C_1-C_6alkoxy or amino;

R^4 is H; hal; hydroxy; amino; C_1-C_6alkyl-amino, di(C_1-C_6alkyl)-amino, C_1-C_6alkyl; C_1-C_6alkoxy which is unsubstituted or mono-, di- or trisubstituted by halogen or hydroxy; C_1-C_6alkoxyC_1-C_6alkoxy; C_1-C_6alkoxyC_1-C_6alkoxyC_1-C_6alkoxy; C_1-C_6alkoxyC_1-C_6alkyl; C_3-C_7cycloalkyl or C_3-C_7cycloalkylC_1-C_6alkoxy that may be substituted at the cycloalkyl residue by C_1-C_6alkyl; C_1-C_6alkoxycarbonyl; C_3-C_6alkenyloxy; (C_1-C_6alkyl)$_2$N-C_1-C_6alkoxy; C_1-C_6alkyl-sulfanyl; C_1-C_6alkyl-sulfanylC_1-C_6alkoxy,  or

-O-$[CH_2]_n$-A wherein A represents



Y represents O or NR^{13},

and n is 0, 1, 2, 3, 4, 5 or 6;

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R^7 and R^8, independently, are H or C_1-C_6alkyl;

R^9 and R^{10}, independently, are H or hal;

R^{11} is H; hal; C_1-C_6alkoxy; or C_1-C_6alkyl;

R^{12} is H; hal; C_1-C_6alkoxy; or C_1-C_6alkyl;

R^{13} is H or C_1-C_6alkyl;

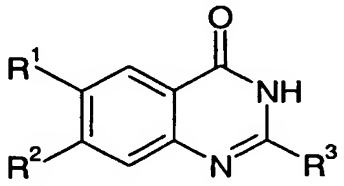
R^{14} is H; hal; C_1-C_6alkoxy; or C_1-C_6alkyl; and

R^{15} and R^{16}, independently, are H; hal; or C_1-C_6alkyl;

in free base or pharmaceutically acceptable acid addition salt form, for use in the treatment or prevention of a disease or condition in which the vanilloid receptor activation plays a role or is implicated.

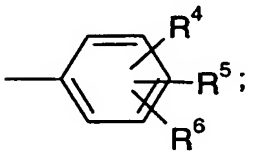
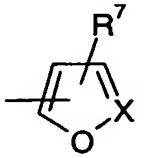
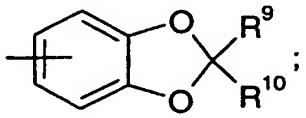
9. A pharmaceutical composition comprising a compound of any one of claims 1 to 4 in free base or pharmaceutically acceptable acid addition salt form, in association with a pharmaceutical carrier or diluent.

10. The use of a quinazolinone of formula I



(I)

wherein

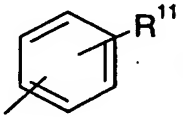
R^1 is hal;  ;  or  ;

X is N or CR^8;

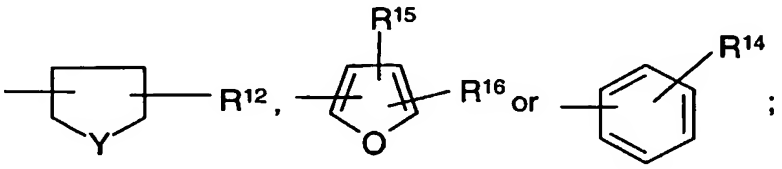
R^2 is hal; nitro; C_1-C_6alkylcarbonyl; C_1-C_6alkyl or C_3-C_6cycloalkyl;

R^3 is C_1-C_6alkyl; C_1-C_6alkoxy or amino;

R^4 is H; hal; hydroxy; amino; C_1-C_6alkyl-amino, di(C_1-C_6alkyl)-amino, C_1-C_6alkyl; C_1-C_6alkoxy which is unsubstituted or mono-, di- or trisubstituted by halogen or hydroxy; C_1-C_6alkoxyC_1-C_6alkoxy; C_1-C_6alkoxyC_1-C_6alkoxyC_1-C_6alkoxy; C_1-C_6alkoxyC_1-C_6alkyl; C_3-

C_7cycloalkyl or C_3-C_7cycloalkylC_1-C_6alkoxy that may be substituted at the cycloalkyl residue by C_1-C_6alkyl; C_1-C_6alkoxycarbonyl; C_3-C_6alkenyloxy; $(C_1$-C_6alkyl$)_2$N-C_1-C_6alkoxy; C_1-C_6alkyl-sulfanyl; C_1-C_6alkyl-sulfanylC_1-C_6alkoxy,  or

-O-$[CH_2]_n$-A wherein A represents



Y represents O or NR^{13},

and n is 0, 1, 2, 3, 4, 5 or 6;

R^5 and R^6, independently, are H; hal; C_1-C_6alkoxy; or C_1-C_6alkyl;

R^7 and R^8, independently, are H or C_1-C_6alkyl;

R^9 and R^{10}, independently, are H or hal;

R^{11} is H; hal; C_1-C_6alkoxy; or C_1-C_6alkyl;

R^{12} is H; hal; C_1-C_6alkoxy; or C_1-C_6alkyl;

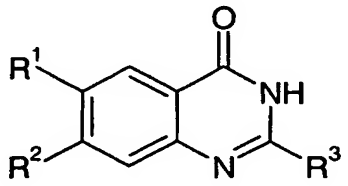
R^{13} is H or C_1-C_6alkyl;

R^{14} is H; hal; C_1-C_6alkoxy; or C_1-C_6alkyl; and

R^{15} and R^{16}, independently, are H; hal; or C_1-C_6alkyl;

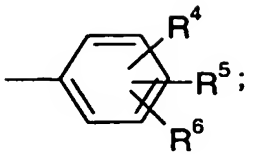
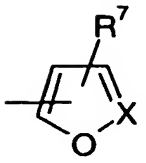
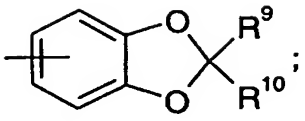
in free base or pharmaceutically acceptable acid addition salt form, as a pharmaceutical for the treatment or prevention of a disease or condition in which vanilloid receptor activation plays a role or is implicated.

11. The use of a quinazolinone of formula I



(I)

wherein

R^1 is hal;  ;  or  ;

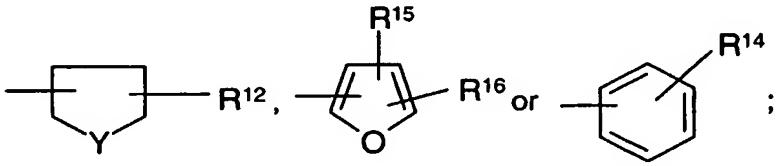
X is N or CR^8;

R^2 is hal; nitro; C_1-C_6alkylcarbonyl; C_1-C_6alkyl or C_3-C_6cycloalkyl;

R^3 is C_1-C_6alkyl; C_1-C_6alkoxy or amino;

R^4 is H; hal; hydroxy; amino; C_1-C_6alkyl-amino, di(C_1-C_6alkyl)-amino, C_1-C_6alkyl; C_1-C_6alkoxy which is unsubstituted or mono-, di- or trisubstituted by halogen or hydroxy; C_1-C_6alkoxyC_1-C_6alkoxy; C_1-C_6alkoxyC_1-C_6alkoxyC_1-C_6alkoxy; C_1-C_6alkoxyC_1-C_6alkyl; C_3-C_7cycloalkyl or C_3-C_7cycloalkylC_1-C_6alkoxy that may be substituted at the cycloalkyl residue by C_1-C_6alkyl; C_1-C_6alkoxycarbonyl; C_3-C_6alkenyloxy; (C_1-C_6alkyl)$_2$N-C_1-C_6alkoxy; C_1-C_6alkyl-sulfanyl; C_1-C_6alkyl-sulfanylC_1-C_6alkoxy,  or

-O-$[CH_2]_n$-A wherein A represents



Y represents O or NR^{13},

and n is 0, 1, 2, 3, 4, 5 or 6;

R^5 and R^6, independently, are H; hal; C_1-C_6alkoxy; or C_1-C_6alkyl;

R^7 and R^8, independently, are H or C_1-C_6alkyl;

R^9 and R^{10}, independently, are H or hal;

R^{11} is H; hal; C_1-C_6alkoxy; or C_1-C_6alkyl;

R^{12} is H; hal; C_1-C_6alkoxy; or C_1-C_6alkyl;

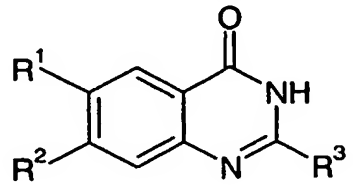
R^{13} is H or C_1-C_6alkyl;

R^{14} is H; hal; C_1-C_6alkoxy; or C_1-C_6alkyl; and

R^{15} and R^{16}, independently, are H; hal; or C_1-C_6alkyl;

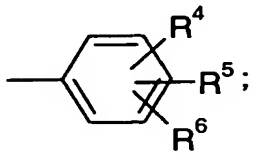
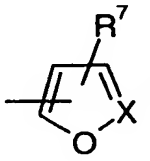
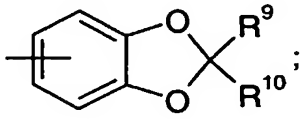
in free base or pharmaceutically acceptable acid addition salt form, for the manufacture of a medicament for the treatment or prevention of a disease or condition in which vanilloid receptor activation plays a role or is implicated.

12. A method for treating or preventing a disease or condition in which vanilloid receptor activation plays a role or is implicated comprising administering to a mammal in need thereof a therapeutically effective amount of a quinazolinone of formula I



(I)

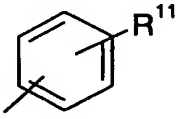
wherein

R^1 is hal;  ;  or  ;

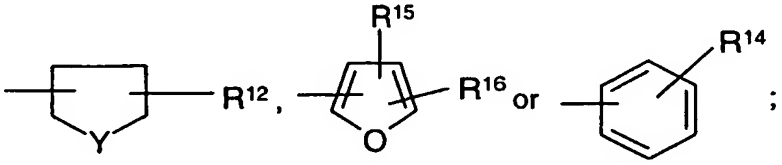
X is N or CR^8;

R^2 is hal; nitro; C_1-C_6alkylcarbonyl; C_1-C_6alkyl or C_3-C_6cycloalkyl;

R^3 is C_1-C_6alkyl; C_1-C_6alkoxy or amino;

R^4 is H; hal; hydroxy; amino; C_1-C_6alkyl-amino, di(C_1-C_6alkyl)-amino, C_1-C_6alkyl; C_1-C_6alkoxy which is unsubstituted or mono-, di- or trisubstituted by halogen or hydroxy; C_1-C_6alkoxyC_1-C_6alkoxy; C_1-C_6alkoxyC_1-C_6alkoxyC_1-C_6alkoxy; C_1-C_6alkoxyC_1-C_6alkyl; C_3-C_7cycloalkyl or C_3-C_7cycloalkylC_1-C_6alkoxy that may be substituted at the cycloalkyl residue by C_1-C_6alkyl; C_1-C_6alkoxycarbonyl; C_3-C_6alkenyloxy; (C_1-C_6alkyl)$_2$N-C_1-C_6alkoxy; C_1-C_6alkyl-sulfanyl; C_1-C_6alkyl-sulfanylC_1-C_6alkoxy,  or

-O-$[CH_2]_n$-A wherein A represents



Y represents O or NR^{13},

and n is 0, 1, 2, 3, 4, 5 or 6;

R^5 and R^6, independently, are H; hal; C_1-C_6alkoxy; or C_1-C_6alkyl;

R^7 and R^8, independently, are H or C_1-C_6alkyl;

R^9 and R^{10}, independently, are H or hal;

R^{11} is H; hal; C_1-C_6alkoxy; or C_1-C_6alkyl;

R^{12} is H; hal; C_1-C_6alkoxy; or C_1-C_6alkyl;

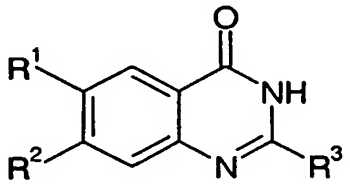
R^{13} is H or C_1-C_6alkyl;

R^{14} is H; hal; C_1-C_6alkoxy; or C_1-C_6alkyl; and

R^{15} and R^{16}, independently, are H; hal; or C_1-C_6alkyl;

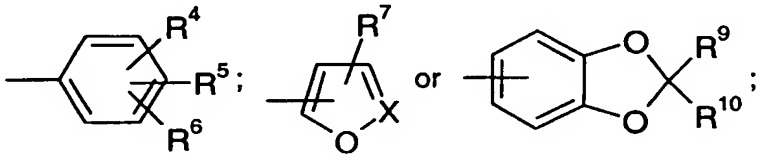
in free base or pharmaceutically acceptable acid addition salt form.

13. A pharmaceutical composition for the treatment or prevention of a diseases or condition in which vanilloid receptor activation plays a role or is implicated comprising a quinazolinone of formula I



(I)

wherein

R^1 is hal;  ;

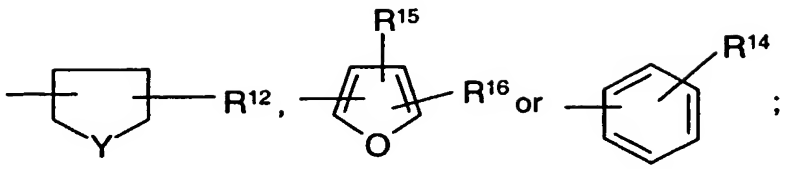
X is N or CR^8;

R^2 is hal; nitro; C_1-C_6alkylcarbonyl; C_1-C_6alkyl or C_3-C_6cycloalkyl;

R^3 is C_1-C_6alkyl; C_1-C_6alkoxy or amino;

R^4 is H; hal; hydroxy; amino; C_1-C_6alkyl-amino, di(C_1-C_6alkyl)-amino, C_1-C_6alkyl; C_1-C_6alkoxy which is unsubstituted or mono-, di- or trisubstituted by halogen or hydroxy; C_1-C_6alkoxyC_1-C_6alkoxy; C_1-C_6alkoxyC_1-C_6alkoxyC_1-C_6alkoxy; C_1-C_6alkoxyC_1-C_6alkyl; C_3-C_7cycloalkyl or C_3-C_7cycloalkylC_1-C_6alkoxy that may be substituted at the cycloalkyl residue by C_1-C_6alkyl; C_1-C_6alkoxycarbonyl; C_3-C_6alkenyloxy; (C_1-C_6alkyl)$_2$N-C_1-C_6alkoxy; C_1-C_6alkyl-sulfanyl; C_1-C_6alkyl-sulfanylC_1-C_6alkoxy,  or

-O-$[CH_2]_n$-A wherein A represents



Y represents O or NR^{13},

and n is 0, 1, 2, 3, 4, 5 or 6;

R^5 and R^6, independently, are H; hal; C_1-C_6alkoxy; or C_1-C_6alkyl;

R^7 and R^8, independently, are H or C_1-C_6alkyl;

R^9 and R^{10}, independently, are H or hal;

R^{11} is H; hal; C_1-C_6alkoxy; or C_1-C_6alkyl;

R^{12} is H; hal; C_1-C_6alkoxy; or C_1-C_6alkyl;

R^{13} is H or C_1-C_6alkyl;

R^{14} is H; hal; C_1-C_6alkoxy; or C_1-C_6alkyl; and

R^{15} and R^{16}, independently, are H; hal; or C_1-C_6alkyl;

and a carrier.